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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/132,521	08/11/98	NAGAI	[illegible]

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EXAMINER
STRUDP,C

ART UNIT	PAPER NUMBER
1633	5

DATE MAILED: 04/14/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/132,521	Nagai et al.
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-13* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-13* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

No claims allowed for the reasons set forth below.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 9 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants' claimed invention is to an *in vivo* method and a pharmaceutical composition for conducting gene therapy for the treatment of HIV in which a recombinant Sendai virus vector is administered to deliver stromal cell-derived factor (SDF-1) alpha or beta to block the T-cell CXC-chemokine receptor-4 and prevent cellular infection by HIV. Applicants have provided no teachings or examples specific to *in vivo* gene therapy with the exception of the appropriate dose (pg 9, para. 1). For example, Applicants have provided no teachings on the route of administration, methods of targeting infected tissue (e.g., how to deliver to lymph nodes

during latent phase of the disease), appropriate target tissue for each stage of the disease, method of ensuring and monitoring efficient and stable gene expression, and method of evaluating the effectiveness of the treatment. (Miller et al and Anderson et al, full article).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation or resolved using animal models or *in vitro* studies. These include the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc...), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level and stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (Eck et al, pg 81, col 2, para 3-pg 82, col 1, para. 2; & Verma et al, full article). Because Applicant has not provided the specifics to the use of the recombinant Sendai virus or SDF-1 for conducting gene therapy in the treatment of HIV, it would have required one of ordinary skill in the art at the time of the invention undue experimentation to practice the claimed invention.

Claim 13 is to a method of inhibiting HIV proliferation by incubating HIV-infected cells with a recombinant Sendai virus vector. The meaning of the term "proliferation" in the context of the claimed invention is interpreted to be the ceasing of the replication in HIV-infected cells. For this reason then claim is not enabled for a method of use because production of SDF-1 would only

block the entry of HIV into non-infected cells. It would have no effect on T-cells that were already infected and in which the virus was actively replicating or latent (Bangham et al., pg 1619, col. 1, para 3). The claim also reads on use *in vivo* and therefore for the reasons previously stated it is not enabled for the method of use.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 4, 5, and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 5, 11, and 12 are unclear as to the meaning of "disseminative" and "not disseminative".

Claim 13 is unclear as to the meaning and context of the use of the terms "proliferation" and "incubation". Does proliferation halt HIV replication and/or infection of healthy cells? Is incubation part of an *in vitro* and/or *in vivo* method of treatment?

Claim Rejections - 35 USC § 103

5. Claims 1-8 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Hasan et al. (1997) or Yu et al. (1997), in view of both of Bleul et al. (1996) and Calain et al (1993).

Applicants' claimed invention is to a recombinant Sendai virus vector expressing stromal cell-derived factor, a pharmaceutical composition containing said vector with a carrier, and a method for its use in the treatment of HIV.

Bleul et al. teach that SDF-1 inhibits infection of HeLa-CD4 cells, CXCR-4 transfectants, and peripheral blood mononuclear cells by T-tropic HIV (abstract). Bleul et al does not teach its production from a recombinant Sendai virus vector.

Hasan et al. and Yu et al. teach the use of recombinant Sendai virus for expressing firefly luciferase and gp120, respectively. Hasan et al. and Yu et al. do not teach the use of the virus vector for expressing SDF-1 in the treatment of HIV nor specifically assert the use of centrifugation to recover the encoded gene.

Calain et al. teach the use of centrifugation (45 minutes, 12,000 * g) to recover the Sendai virus nucleocapsids originating from pSV-DI-H4 plasmids. Calain et al does not teach the use of recombinant Sendai virus for encoding SDF-1.

In light of Bleul et al., Hasan et al., Yu et al. and Calain et al it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the recombinant Sendai virus vector for expressing SDF-1 in the treatment of HIV because of the high level of infectious viral recovery afforded by this vector (Hasan et al., pg 2813, col. 2, para. 2) and to utilize

centrifugation for the purpose of causing cell lysis in order to recover SDF-1. Because the pharmaceutical composition contains said vector and a carrier, which by definition is any immuno-tolerant solution (e.g., water, saline, tris, ...) and is therefore given no patentable weight, it to is obvious.

6. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bleul et al (1996), Hasan et al (1997) and Hasegawa et al (1997, WO 97/16539).

Applicants' claimed invention is to a method of *ex vivo* gene therapy for HIV utilizing a recombinant Sendai virus vector expressing stromal cell-derived factor (SDF-1).

Bleul et al. teach that SDF-1 inhibits infection of HeLa-CD4 cells, CXCR-4 transfectants, and peripheral blood mononuclear cells by T-tropic HIV (abstract). Bleul et al does not teach its production from a recombinant Sendai virus vector.

Hasan et al. teach the use of recombinant Sendai virus for efficacious and high levels of expression of the firefly luciferase gene, which was inserted immediately before the origin of replication of the viral 3'-proximal nucleocapsid (N) protein gene (abstract). Hasan et al does not teach its use in gene therapy.

Hasegawa et al. teach the use of a recombinant Sendai virus in gene therapy for the purpose of expressing the encoded gene.

In light of Bleul et al., Hasan et al., and Hasegawa et al. it would have been obvious to one of ordinary skill in the art at the time of the invention to have used recombinant Sendai virus

encoding SDF-1 for the purpose of conducting efficacious *ex vivo* gene therapy in the treatment of HIV with a viral system that has high expression rates.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached at (703) 308-2801. The fax number for this Group is (703) 308-0294.

Carrie Stroup
7 April 1999

BRIAN R. STANTON, PH.D
PRIMARY EXAMINER